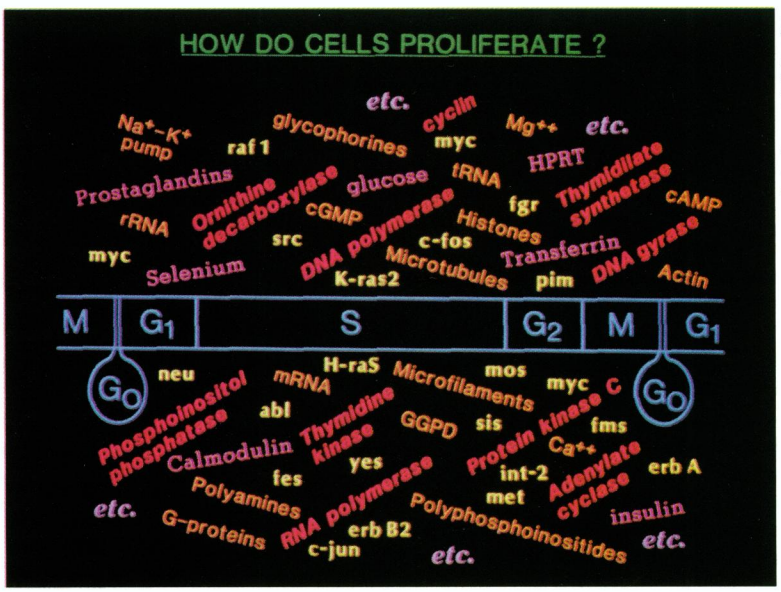
Ambivalent Antihistamines

Warding off allergies with antihistamines may prove to be dangerous for allergy sufferers, if recent studies on mice are any indication. The study found that three widely used antihistamines stimulate tumor growth in mice.

Lorne Brandes and colleagues at the Manitoba Institute of Cell Biology at the University of Manitoba in Winnipeg, Canada, injected tumor culture lines into mice and then administered antihistamines daily in varying estimated human-equivalent doses for 18–21 days. The researchers then sacrificed the mice and surgically removed the tumors. In comparing the weights of the tumors, they found that three of the five antihistamines tested caused the tumors to grow heavier. This innovative method differs from traditional tests for carcinogenicity, which involve administering a substance to healthy laboratory animals; as a result, the study's conclusions are being questioned.

The three antihistamines that were found to cause the existing tumors in the mice to grow larger are loratadine, which is used in Claritin, made by Schering-Plough of Madison, New Jersey; astemizole, the main ingredient in Hismanal, made by Janssen Pharmaceutica Inc. of Titusville, New Jersey; and hydroxyzine, used in Atarax, made by the Roerig Division of Pfizer Inc. of New York. Following the publication of the study, the manufacturers of these drugs issued statements defending their products and criticizing the researchers' human risk assessment methods.



Carlos Sonnenschein/Ana Soto

Cancer chaos. There are as many theories on how cancer is caused as there are scientists studying it.

The two other drugs tested in the study were cetrizine, which is used in Reactine, also made by Pfizer, and doxylamine, used in over-the-counter drugs such as NyQuil and Unisom, which were not found to stimulate tumor growth.

The researchers defend their methods in the report of the study, saying, "Although the potential for carcinogenicity has received considerable attention in preclinical drug testing in rodents, the propensity of pharmaceuticals to enhance the growth of existing tumors or the development of malignancy induced by chemical or viral initiators has been neglected."

The study was published in the 18 May 1994 issue of the *Journal of the National Cancer Institute* along with an editorial written by Douglas L. Weed, of the Preventive Oncology Branch, Division of Cancer Prevention and Control, of the National Cancer Institute. Weed raised questions about the human risk assessment methods that were involved in the study and called for further research, recommending that no immediate changes be made in the use of the antihistamines.

Brandes had called on the Food and Drug Administration to change the labeling on the antihistamines, but the FDA said such a move would be premature. In a press release, the agency said that standard carcinogenicity tests with the antihistamines in mice and rats do not demonstrate carcinogenicity and the FDA believes that further study is needed before any action is taken. The FDA advised consumers that short term use of the antihistamines is not at issue.

The agency is taking the study seriously, however. Researchers at the FDA plan to duplicate the study and reevaluate the human risk assessment methods. According to Joseph DeGeorge, supervisory pharmacologist in the Division of Oncology and Pulmonary Drug Products at the FDA, researchers will not only duplicate the study, but will extend their research to include modifications to Brandes' work. For example, DeGeorge said that human tumors may different than the tumor types that Brandes used. "We are trying to extend to other tumor types and other assays." The FDA is interacting very closely with Brandes in duplicating his work, DeGeorge said.

The FDA will also examine another innovative method used in Brandes' study pertaining to how tumors respond to increasing doses of antihistamines. Brandes found that the dose–response rate forms a bell curve, with little response at low doses and high doses, and heavy response at mid-sized doses. In the past, researchers have generally assumed that response increases linearly as dose increases.

Brandes' finding implies that traditional research involving only the administration of high doses could have missed high levels of response at mid-sized doses.

Meeting of the Cancer Minds

A recent meeting brought together scientists conducting cancer research using information gained from studies using species "ranging from bacteria to yeast to fruit flies to mice to humans," as described by Richard Paules, coordinator of the conference on Molecular Mechanisms of Environmental Carcinogenesis. The meeting, held at the NIEHS September 19–20, was a chance for researchers from diverse areas to present the most recent advancements in environmental cancer reseach.

Perhaps the most exciting and certainly the most publicized information presented at the conference was the isolation of *BRCA1*, the gene for inherited susceptibility to breast cancer by a team of researchers from several institutions including the NIEHS and the University of Utah School of Medicine. Several other presentations highlighted recent advance in cancer knowledge in such areas as the varying consequences of genetic damage in animals with different genetic backgrounds; the correlation between the appearance of Li-Fraumeni syndrome in young children caused by genetic mutations in the p53 gene and the appearance of cancers from the same type of mutations in their parents and grandparents later in life; identification of a mutation in an area of chromosome 14q which may be developed as a prognostic tool for endometrial cancer; and an update on research of the effect of exogenous estrogens on rates of endometrial and breast cancers.

Researcher Amy Moser of the McArdle Laboratory for Cancer Research at the University of Wisconsin School of Medicine presented studies supporting the theory that particular genetic mutations, in combination with particular environmental toxicants, may result in different consequences; for example, mutations may produce a lot of tumors or no tumors depending on the genetic makeup of the individual in which they occur. Moser's studies